Scleromyxedema

A Case Clinically and Histologically Responsive to Intravenous Immunoglobulin

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ABSTRACT

The authors report a 60-year-old man who presented with a rash and developed ataxia, confusion, slurring of speech, and disorientation that prompted hospitalization. A diagnosis of generalized scleromyxedema with neurological features was eventually made and the patient was treated with intravenous immunoglobulin. The patient showed clinical response to intravenous immunoglobulin therapy, and repeat biopsy showed histological clearance of increased fibroblasts and mucin deposition, demonstrating both clinical and histological response to intravenous immunoglobulin.
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A 60-year-old man presented to the hospital with a rash and new onset neurological symptoms. The rash began three months prior to hospitalization, starting on the nasal bridge and then progressing to involve his ears and cheeks. He had initially been treated with topical steroids and trimethoprim-sulfamethoxazole without improvement. He began having difficulties with his gait, his speech, and his mentation and was taken to the hospital.

On admission, extensive work-up revealed no significant acute findings, and a presumed diagnosis of viral encephalitis was made. A skin biopsy performed on left dorsal hand in the hospital revealed only perivascular dermatitits with mild focal interface change consistent with viral exanthem. He received systemic steroids during his admission in addition to antibiotics and made a full recovery from his neurological deficits and skin lesions.

Approximately two months after discharge, the rash reappeared on his face and arms. On presentation to the authors' office, he complained of a very tight feeling with swelling and puffiness on his face with wrinkling of the forehead and the cheeks (Figures 1A and 1B). The rash consisted of several waxy papules on the ears and distal arms. He was also beginning to notice some numbness and tingling in his extremities with some motor weakness in his hands. The presentation and history of neurological problems were concerning for generalized scleromyxedema, and a punch biopsy was performed on the patient's right earlobe and a serum protein electrophoresis was obtained. The biopsy confirmed the diagnosis of scleromyxedema and serum protein electrophoresis (SPEP) indicated elevated immunoglobulin G (IgG) as suspected.

The patient was started on intravenous immunoglobulin (IVIG) therapy, receiving two infusions per month for six months. He tolerated treatments during these six cycles and his skin improved. He had decreased tightness of skin and no erythema or papules noted on exam (Figures 2A and 2B). He was able to have a firm grip and did not have any paresthesias. Biopsy and SPEP were repeated in December of 2010. Biopsy indicated dermal sclerosis, but no increase in fibroblasts, and alcian blue stain showed no increase in dermal mucin. SPEP indicated that IgG was still elevated as was suspected. The patient did not have any therapy from January 14, 2010, to June 14, 2010, but noted significant increase in skin tightness and high-dose IVIG treatment was resumed for six more cycles. He was maintained on IVIG therapy at a reduced dose of one infusion per month. He tolerated therapy well with no evidence of skin tightening or recurrent papules. After six months at lower dose, further IVIG therapy was held. Following initial hospitalization and during treatment, the patient experienced no neurological signs or symptoms.

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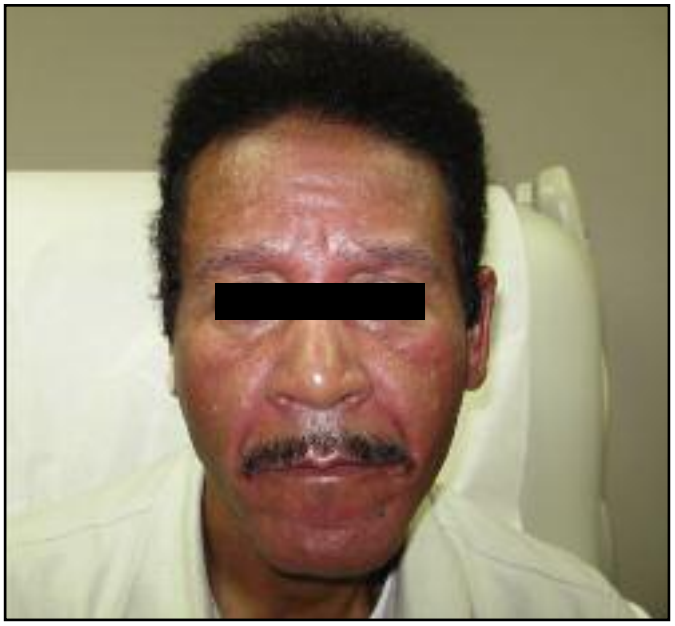
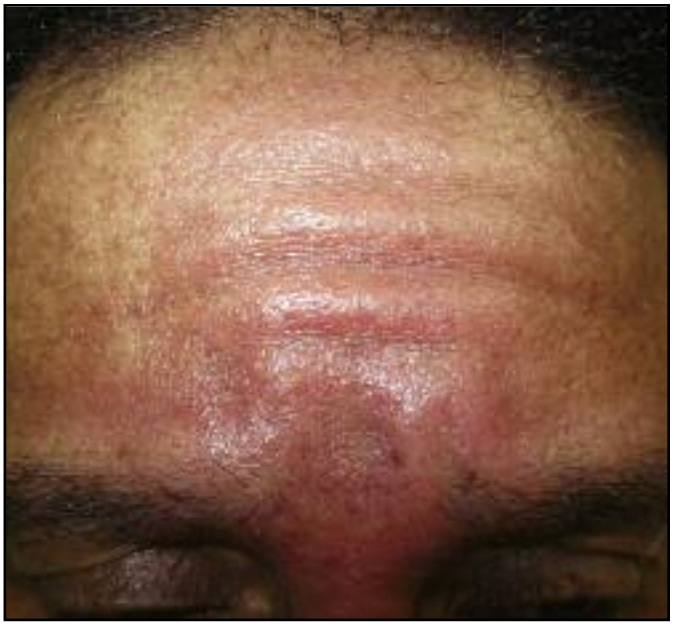



Figures 1A and 1B. On presentation to the authors' office, the patient complained of a very tight feeling with swelling and puffiness on his face with wrinkling of the forehead and the cheeks

DISCUSSION

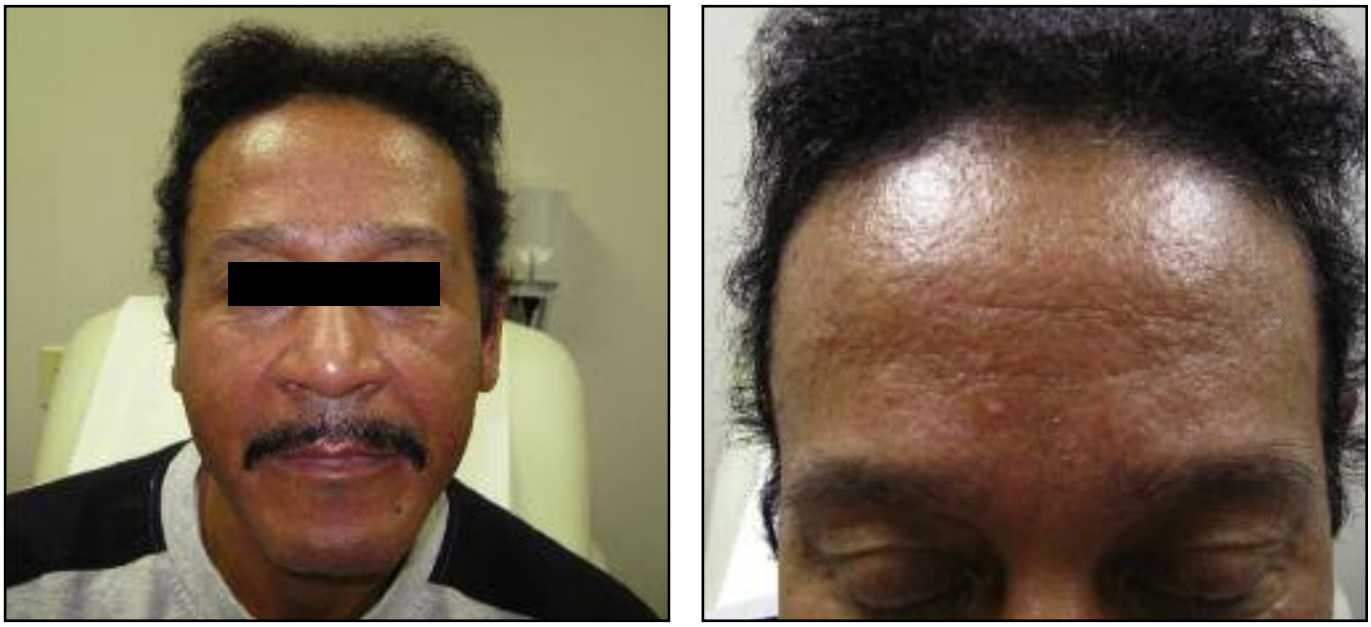
Scleromyxedema is a rare disorder of unknown etiology. Typical presentation is a rash involving the head, neck, and upper extremities. The rash normally includes flesh-colored waxy, firm papules often in a linear array.[4] Bolognia indicates the following four diagnostic criteria: generalized papular eruption and sclerodermoid, microscopic triad (mucin deposition, fibroblast proliferation, fibrosis), monoclonal gammopathy, and absence of thyroid disease.[2,5]

On biopsy, the specimen will have "extensive mucin deposition throughout the dermis, an increased number of irregularly arranged fibroblast-like cells, separation of collagen bundles, and an increase in the number of inflammatory cells." Mucin and hyaluronic acid are produced by both fibroblasts and mast cells and this production is increased during disease processes. Hyaluronic acid is hydrophilic, thus absorbing large amounts of water leading to myxedema.[1] With continued swelling and mucin production, the dermis and subcutaneous tissue begin producing excessive collagen leading to fibrosis. This excess collagen causes the scleroderma-like appearance.[1] To identify the mucin, alcian blue, toluidine blue, and colloidal iron may be used.[1,5,10] In suspecting a mucinous disease, the specimen can be fixed in ethanol to improve detection of mucin. In older lesions, collagen bundles are prominent and more likely to show effacement of the epidermis due to underlying fibrosis and mucin deposition.[1,10] Scleromyxedema varies from lichen myxedematous in diffuse skin involvement versus local, IgG paraproteinemia and systemic involvement.[4]

Patients may have features similar to scleroderma, including esophageal dysmotility, restrictive lung disease, muscle weakness, sclerodactyly, and skin tightening. Labs indicate an IgG gamma light chain monoclonal gammopathy, and significance of this finding on etiology is unknown.[2,4,6,9] Bone marrow biopsy, if done, may show elevated plasma cells; progression to multiple myeloma is possible and occurs in ~10 percent of affected people. Rarely patients may have neurological symptoms that begin with a flu-like prodrome, including gait disturbances, seizures, encephalitis, and decreased level of consciousness.[4,5] Typically, neurological abnormalities do not occur initially, but on exacerbations of cutaneous disease.[6]

Etiology of the disease is unclear, as mentioned above. One case showed that autopsy found no increased deposition of mucin in organs including muscle, indicating another mechanism is likely for fibroplast proliferation.[2,8] Another study indicated that "purified immunoglobulin from the serum" failed to stimulate fibroplast proliferation/growth; thus, it is unknown if the paraproteinemia seen in affected patients has a direct role in etiology and it appears not.[5] Patients, such as the one described in this case, treated with IVIG continue to have the elevated paraproteinemia following and during treatment, but have resolution of cutaneous and extracutaneous manifestations.[2,8] Recent research proved that interleukin (IL)-6 production is increased and blood-brain barrier function is altered in patient's with central nervous system manifestations.[4,6] Lack of understanding of etiology makes treatment difficult.

Possible treatments include "melphalan, interferon alpha, autologous stem-cell transplantation, thalidomide, high-dose dexamethasone, cyclophosphamide, plasma-pheresis and IVIG."[2,5] The side effects limit the use of many. IVIG has mild side effects typically; although fatal side effects including



Figures 2A and 2B. The patient had decreased tightness of skin and no erythema or papules noted on exam after receiving two infusions per month for six months of intravenous immunoglobulin (IVIG) therapy. He tolerated treatments during these six cycles and his skin improved.

anaphylaxis, acute renal failure, and deep venous thrombosis/pulmonary embolism/stroke may occur.[2,5] Acetaminophen and diphenhydramine are commonly given prophylactically prior to infusion to prevent headaches, urticaria, and fevers. Some believe that IVIG may exert its effects by blocking the Fc receptor, making phagocytic cells nonfunctional.[2] One study states that IVIG neutralizes "pathogenic autoantibodies by idiotypic and anti-idiotypic antibodies," leading to effects on dendritic cells and the complement pathway. Others believe that IVIG alters metalloproteinases, resulting in alteration of matrix collagen. If IVIG truly blocks the Fc receptor, this can explain why the paraproteinemia does not resolve and why "maintenance infusions" are necessary for continued clearance.[2,7]

Much research is needed both on scleromyxedema and on IVIG to determine etiology of disease and to determine mechanism of action of IVIG. Currently, IVIG is a well-tolerated, successful treatment for scleromyxedema. From research reviews and from the case presented herein, maintenance infusions appear a necessity.

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